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Brain Mapping with Functional MR Imaging: Comparison of Gradient-Echo–based Exogenous and Endogenous Contrast Techniques[1]

PURPOSE: **To compare directly the two most widely used methods of functional magnetic resonance (MR) imaging—dynamic contrast material–enhanced MR imaging and blood oxygenation level–dependent (BOLD) MR imaging.**

MATERIALS AND METHODS: **Five healthy volunteers underwent dynamic contrast-enhanced and BOLD MR imaging with a conventional 1.5-T MR unit during visual stimulation and a dark control state. BOLD studies were performed with a gradient-echo sequence, and dynamic MR imaging was performed with an echo-shifted gradient-echo sequence after intravenous administration of a bolus of gadopentetate dimeglumine.**

RESULTS: **A significantly greater percentage signal change was found with dynamic MR imaging than with the BOLD technique. The extent of area activated was also significantly greater.**

CONCLUSION: **With standard clinical imagers and these gradient-echo–based techniques, greater percentage activation and area of activation can be achieved with dynamic MR imaging than with BOLD MR imaging.**

Index terms: Blood, flow dynamics, 10.919 • Brain, function, 10.919 • Brain, MR, 17.121412, 17.121416, 17.12144 • Magnetic resonance (MR), rapid imaging

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During the past decade, nuclear medicine imaging techniques such as positron emission tomography have greatly enhanced our ability to study the physiologic characteristics of human brain. These techniques, however, are limited by the need for radioactive tracers, high operating costs, and limited spatial and temporal resolution.

In 1991, Belliveau et al (1) described an alternative functional imaging technique that uses fast magnetic resonance (MR) imaging to map stimulation of the visual cortex. This approach represents a new method to study brain physiology with superior temporal and spatial resolution and without ionizing radiation. In their study, subsecond echo-planar MR imaging was used in conjunction with intravenous injection of a bolus of paramagnetic contrast material (gadopentetate dimeglumine) to measure relative cerebral blood volume (CBV) changes in the occipital cortex during visual stimulation.

Subsequent studies have confirmed this result by using gradient-echo (GRE) techniques (2–4) with a conventional 1.5-T MR unit. One of these methods, the echo-shifted fast low-angle shot (FLASH) technique, is particularly suited for dynamic MR imaging studies as it is especially sensitive to changes in T2* that reflect subtle magnetic field inhomogeneities induced when the contrast agent passes through the vascular compartments (3–5). Within this pulse sequence, the excitation of spins and measurement of their gradient-recalled echoes are achieved in successive repetition time periods, which substantially enhances the T2* weighting without loss in temporal resolution.

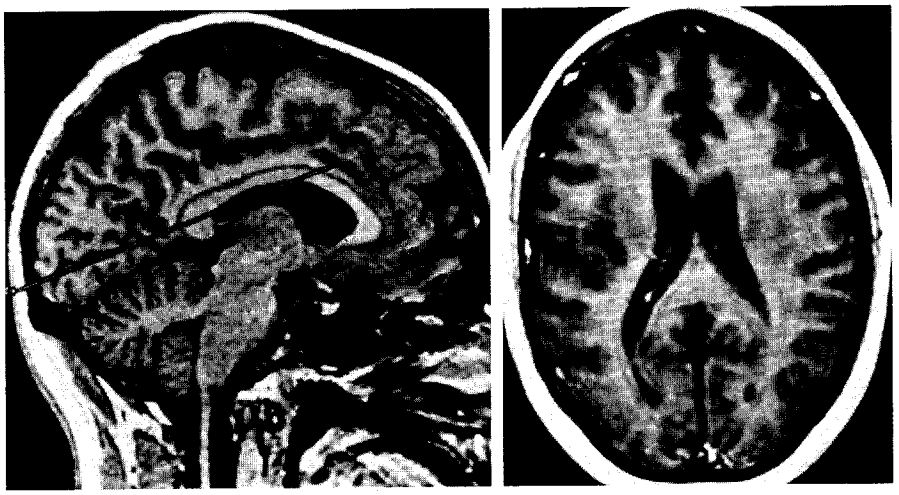
In addition to the dynamic MR imaging mapping approach, a newer functional MR technique called blood oxygenation level–dependent (BOLD) imaging (6–13) has emerged. This method is noninvasive, has the advantage of unlimited repeatability, and has become the more widely applied method for brain mapping with MR imaging. The BOLD technique was initially described by Ogawa et al (7), who used GRE imaging, as a method dependent on small changes in the steady-state level of paramagnetic deoxygenated hemoglobin. More recently, however, it has been shown that other factors such as inflow (14) and draining venules (15) may contribute to the signal intensity change observed with this technique with use of GRE pulse sequences and large flip angles. BOLD imaging is also influenced by other uncontrolled physiologic parameters such as hematocrit level, oxygen saturation, cerebral blood flow, and CBV. Because questions have been raised about the contribution of other effects (eg, inflow and draining venules) to signal intensity changes seen with BOLD imaging (14,15), we will continue to use the acronym BOLD throughout this article but acknowledge that effects may not be related solely to deoxygenation.

Since its introduction, functional MR imaging during various sensorimotor and cognitive activation procedures has been performed with one of these two methods (1–13). To date, there has not been a study comparing the results of these two methods directly. The purpose of our study was to make a direct comparison of BOLD and dynamic MR imaging methods to determine the relative changes in signal intensity with stimulation and the anatomic extent of activation and compare the relative advantages and limitations of these methods.

Abbreviations: BOLD = blood oxygenation level dependent, CBV = cerebral blood volume, FLASH = fast low-angle shot, GRE = gradient echo, NCC = normalized cross correlation, ROI = region of interest.

MATERIALS AND METHODS

This study was approved for human subjects by the Intramural Research Review Board of the National Institute of Mental Health, National Institutes of Health, Bethesda, Md. Informed consent was obtained from all subjects. Five healthy volunteers were studied with a 1.5-T MR imager (Signa; GE Medical Systems, Milwaukee, Wis) equipped with a standard quadrature head coil. For a fair, unbiased comparison, functional MR imaging was performed with both dynamic and BOLD imaging methods in a single session during visual stimulation and a dark resting state. Visual activation was induced by photic light projected at 7.8 Hz by means of a back-projection video system (Resonance Technology, Woodland Hills, Calif). BOLD imaging was performed before dynamic MR imaging to preclude any possible effects of the contrast agent on the BOLD study.



a. b.

Figure 1. Subject 4. **(a)** Midsagittal localizer image. A line is drawn along the calcarine fissure. **(b)** Oblique high-resolution T1-weighted anatomic image obtained in a plane aligned along the calcarine fissure.

Data Acquisition

For anatomic imaging, a conventional spin-echo pulse sequence was first performed in the midsagittal plane (Fig 1a) to localize the calcarine fissure. Oblique high-resolution, T1-weighted anatomic images (Fig 1b) were then obtained in a plane aligned along the calcarine fissure. BOLD imaging commenced at the same section location by using a GRE sequence with a repetition time of 72 msec, echo time of 60 msec (72/60), flip angle of 10°, field of view of 240 mm, matrix of 128 × 128, and section thickness of 6 mm. This sequence was chosen because of its established application as reported in the literature (9). Thirty-eight sequential images were obtained with a temporal resolution of 12 seconds per image. Six sequential cycles with six images per cycle were obtained with the stimulus on (photic stimulation) cycle alternating with stimulus off (resting) cycles. The sequence of on and off cycles was counterbalanced among subjects. Because of the instability of signal before a steady state is reached, the first two images of the study were routinely discarded in all five subjects.

Dynamic MR imaging was then performed at the same location with an echo-shifted FLASH technique (17/25, 10° flip angle, 240-mm field of view, 128 × 128 matrix, 6-mm section thickness) (3). Sixty contiguous images were obtained with a temporal resolution of 2 seconds per image during both stimulated and unstimulated conditions. In each condition, a 0.2 mmol/kg bolus of gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ) was intravenously administered at the start of the 10th image acquisition at a rate of 6 mL/sec by using a mechanical injector (Medrad, Pittsburgh, Pa) via a 20-gauge catheter placed in the antecubital vein. This was followed by a saline flush. The order of the conditions (photic stimulation and resting dark state) was counterbalanced among subjects, and the two states were separated by at least 15 minutes. Of note, the total dose of gadopentetate dimeglumine used per subject in this study (0.4 mmol/kg) is not approved by the U.S. Food and Drug Administration. It was approved by the Intramural Research Review Board of the National Institute of Mental Health, National Institutes of Health, for research purposes only. All subjects were told of the potential adverse reactions to gadopentetate dimeglumine before informed consent was obtained.

Image Analysis

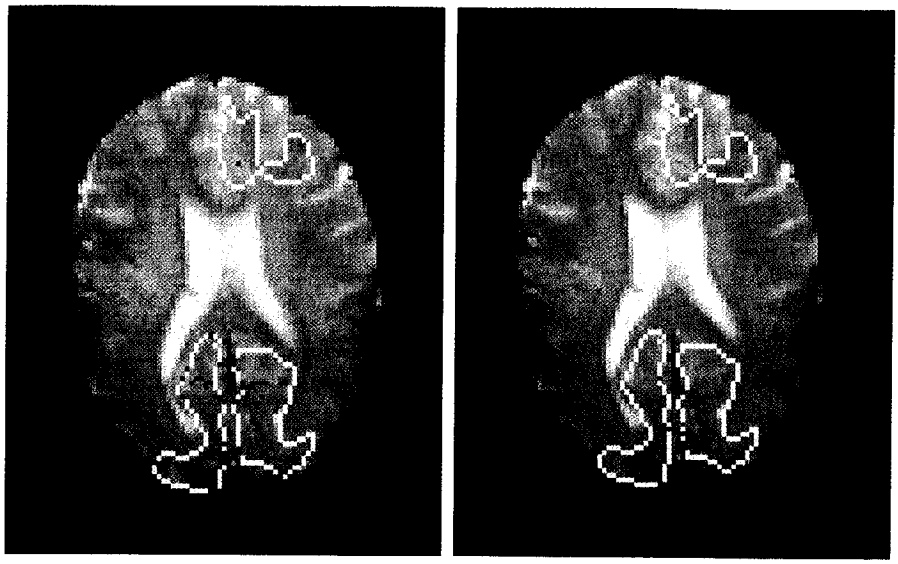
BOLD images were reconstructed by using standard imager software, whereas dynamic MR images were reconstructed off-line. Analysis of both BOLD and dynamic MR images was performed off-line with UNIX-based workstations (Sun Microsystems, Mountain View, Calif) by using Interactive Data Language data processing language (Research Systems, Boulder, Colo). To assess activation, an anatomically based region of interest (ROI) was drawn on the corresponding anatomic image encompassing the entire pericalcarine visual cortex, taking care to exclude visible blood vessels. These ROIs were then applied to the maps of CBV obtained with the dynamic MR imaging technique and to the images obtained with the BOLD technique.

Dynamic MR images were transformed into blood volume maps by applying a pixel-by-pixel statistical analysis through time. First, the background noise on the baseline images obtained before administration of contrast material was determined. This was defined as the extracranial signal intensity during the prebolus phase and was used to set a threshold that facilitated selection of pixels inside the head, while excluding extracranial signal. Only those pixels with a higher signal to noise than the preselected threshold were subjected to further analysis. The signal intensity data in these selected pixels were transformed into concentration values with the following equation: concentration(t) = $-k\ln(S[t]/S_0)$, where $S(t)$ is the signal intensity at time t, S_0 the initial signal intensity (baseline), and k the proportionality constant related to the echo time for each MR image, contrast agent properties, and magnetic field strength. Because our goal was to measure relative CBV during visual stimulation and darkness, it was not necessary to calculate the precise value of k. As an overall multiplicative constant, k cancels out when the ratio of the two states is estimated (2). The concentration versus time series for each pixel was then fitted to a gamma variate function (1,3,4,16,17) to remove recirculation effects that tend to overestimate the area under the first pass. A pixel-by-pixel integration of the fitted curves was used to create the relative CBV maps. Normalized relative CBV maps were then created by taking the ratio of the calculated CBV of each pixel to the mean CBV of all pixels in that section. This normalization of relative CBV maps would annul the effect of any contrast agent if present from the first injection on the ensuing study. The values in these normalized relative CBV (stimulated and unstimulated) maps ranged

Table 1
Results of ROI Analysis

Subject	ROI Area*	Activation: Dynamic MR Imaging	Activation: Bold Imaging
1	77.7	7.0	2.5
2	79.4	11.8	0.9
3	92.8	14.0	1.4
4	87.0	6.4	1.7
5	79.0	9.0	2.4
Mean ± SD	83.2 ± 6.5	9.6 ± 3.2	1.8 ± 0.7

Note.—Data are given as percentages. SD = standard deviation.
* Determined with dynamic MR imaging.



a. b.

Figure 2. Subject 4. GRE MR images obtained with the **(a)** dynamic and **(b)** BOLD techniques show activated pixels (in red) within the anatomic ROIs (in white).

from 0 (arbitrary units) to approximately 2 for parenchymal tissue. Because pixels with signal intensity values more than 3 probably represent vasculature or artifactual signal, we excluded these pixels from further analysis in both stimulated and unstimulated CBV maps.

A difference CBV map was then created for each individual by subtracting the unstimulated normalized relative CBV map from the stimulated normalized relative CBV map.

The BOLD images were subjected to two analyses. First, a difference image was created by subtracting the sum of all the images obtained in the unstimulated state from the sum of all the images obtained in the stimulated state. Second, a normalized cross-correlation (NCC) image was created by cross-correlating, on a pixel-by-pixel basis, the time course of the image signal intensity with a reference vector equivalent to the time course of the stimulation (18,19).

The percentage of signal intensity change or activation was determined for both techniques with analysis of the ROI and analysis of "activated" pixels, as follows.

For the dynamic imaging method, percentage activation was obtained by dividing the blood volume within the ROI of the difference CBV map by the blood volume within the ROI of the unstimulated CBV map and multiplying this value by 100.

For the BOLD method, percentage activation was obtained by dividing the signal intensity within the ROI of the difference image by that within the ROI of the summed image obtained in the unstimulated condition and multiplying this value by 100. Because of differences in data analysis of the two methods and the different underlying physiologic processes being measured, the activated area within the ROI was not identical.

In the creation of CBV maps, use of a preselected threshold to facilitate selection of pixels inside the head while excluding extracranial signal resulted in no blood volume in some of the pixels within the created blood volume maps. Thus, in the calculation of percentage activation for the dynamic MR imaging method, only the pixels with blood volume (and not all the pixels) within the ROI were selected. For the BOLD method, all the pixels in the ROI are available for calculating percentage activation; this can result in underestimation of the percentage activation because of partial voluming. To overcome this bias and to make a fair comparison, the percentage of signal intensity change with the BOLD technique was calculated for each subject in the same number of pixels (with the greatest signal change) within the ROI, as was used for analysis of the dynamic MR images (represented as percentage area within the ROI in the second column of Table 1).

Because neither of the above methods apply equal weight to every pixel in the ROI, the comparative analysis of the ROI as such is potentially misleading. Therefore, a stringent secondary analysis was performed to more accurately account for the individual differences in the analysis of these images.

For the dynamic MR imaging method, we determined an "activation threshold" based on pixel values in a similarly sized frontal ROI (an area presumably not activated by this stimulus) to determine the extent of area activated in the visual cortex. In the difference CBV maps for each individual, activation threshold was identified as the intensity threshold at which no positive signal intensity change or activation was detected in more than 99% of the pixels in the frontal region. On average, more than 99% of the pixels did not show signal intensity change at a mean intensity threshold value of 0.625. This intensity threshold was then applied to the visual ROIs; pixels above this value were considered activated (Fig 2a).

To ensure that the same activation threshold was applied to the BOLD data, we chose an r value from the NCC data that identified less than 1% of the pixels in the frontal region. On average, more than 99% of the pixels in the frontal ROI did not show signal intensity change at a mean r value of .35. An NCC mask of activated pixels in the visual cortex ROI (Fig 2b) was then created by retaining only pixels with an r value of at least .35.

For both methods, percentage activation was calculated in only those pixels that were identified as activated pixels (Table 2, columns 3 and 5).

Extent of activation was computed for both methods as a ratio of the activated pixels to the total number of pixels within the anatomic ROI (Table 2, columns 2 and 4). Statistical analysis was performed by using a matched pair Student t test to compare results from the dynamic MR imaging and BOLD data and between the frontal and occipital ROIs.

RESULTS

Percentage Activation

In the analysis of the ROIs (Table 1), there was a statistically significant difference ($t = 2.8$, $P < .009$) between the two techniques for the percentage activation. The mean relative CBV change for the visual cortex ROI obtained with the dynamic MR imaging method was significantly higher (9.6%; range, 6.4%–11.8%) than the mean signal intensity change with the BOLD technique (1.8%; range, 0.9%–2.5%).

In the analysis of activated pixels (Table 2), the mean signal intensity change in the visual cortex in the BOLD images was significantly lower (9.9%; range, 7.3%–13.6%; $t = 2.8$; $P < .0005$) than the mean relative CBV change obtained with dynamic MR imaging (mean, 101.7%; range, 81%–130%)—even after application of a stringent method to detect activated pixels in the difference CBV maps and NCC images.

Extent of Activation

The extent of area activated was also significantly greater with dynamic MR imaging (mean, 8.3% of ROI; range, 4.5%–15.1%) than with BOLD imaging (mean, 3.1% of ROI; range, 1.3%–3.5%) ($t = 2.8$, $P < .05$).

To test the regional specificity of the functional responses seen with these two methods, comparably sized ROIs were drawn in the frontal region and signal intensity changes in this region were compared with those

in the visual cortex. A significantly greater change in signal intensity was noted with both techniques ($t = 2.8$; $P < .03$ for dynamic MR imaging, $P < .002$ for BOLD imaging) in the visual cortex than in the frontal cortex during visual stimulation. The mean change in signal intensity in the frontal cortex was −4% for dynamic MR imaging and −0.2% for BOLD imaging (Table 3). This indicates that both techniques respect the boundaries of functional neuroanatomy and show only changes specific to the task.

Table 2
Results of Activated Pixel Analysis

	Bold Imaging		Dynamic MR Imaging	
Subject	ROI Area	Activation	ROI Area	Activation
1	2.8	10.7	4.5	110.6
2	3.4	7.3	4.8	93.9
3	3.5	10.2	15.1	130.5
4	4.4	7.5	9.0	92.5
5	1.3	13.6	7.9	81.0
Mean ± SD	3.1 ± 1.2	9.9 ± 2.6	8.3 ± 4.3	101.7 ± 19.3

Note.—Data are given as percentages. SD = standard deviation.

DISCUSSION

Functional MR imaging, with its superior temporal and spatial resolution and greater accessibility, is emerging as a powerful tool in functional brain mapping. Since its advent, this technique has rapidly evolved; the two widely available methods, dynamic and BOLD techniques, have their individual advantages and limitations. To our knowledge, this is the first study comparing these two methods directly. We individualized the GRE pulse sequence for each method on the basis of the likelihood of maximal signal intensity change as reported in the literature (3,4,9). A FLASH pulse sequence adapted by Connelly et al (9) was used for the BOLD method, and an echo-shifted FLASH technique (3,4) was used for the dynamic MR imaging method. The mean percentage signal change obtained with the BOLD method in our study was lower than the relative CBV change observed with dynamic MR imaging. A major contributing factor may be that the magnitude of magnetic susceptibility effects in BOLD contrast is smaller than that produced by exogenous paramagnetic contrast agents; the results of our study support this theory very well.

One of the important differences between the two techniques is in the extent of activation. With the BOLD method, only approximately 3% of the area within the striate cortex ROI showed significant signal intensity changes during photic stimulation. In comparison, the dynamic MR imaging method showed a larger area (mean, 8.3%) of activation. The cortical areas related to vision include the entire expanse of striate cortex (20); flashing light causes increase in relative cerebral blood flow that encompasses the entire region. This suggests that both techniques as employed in this study considerably underestimate the functional neuroanatomy.

It is important to note that our study only addresses single-section acquisitions performed with GRE methods and a standard 1.5-T MR system. Echo-planar imaging, with its superior time resolution, may show different results, and we are currently exploring this. Because single-section methods suffer from the vagaries of section localization, it is likely that on occasion the relevant functional anatomy is primarily out of section. Multisection and three-dimensional volume techniques should be free of this problem (21).

There are other advantages and limitations to each of these two techniques. The number of studies that can be performed with the dynamic MR imaging method in one subject is limited by the dose of gadopentetate dimeglumine, whereas the BOLD method has the advantage of being repeatable a number of times. The interpretation of BOLD images, however, is hampered by the combined effect of several important physiologic parameters (eg, perfusion rate, oxygen consumption, and blood flow). In addition, spoiled GRE–based BOLD imaging has the additional confounding influence of inflow (18) and large vessel effects (19). These effects have raised an important question about what exactly is being imaged with the BOLD technique that is called activation. Does the change in signal intensity with stimulation arise from draining venules or from capillary beds in the parenchyma? Techniques developed in GRE MR imaging to suppress inflow (14) significantly lower the signal to noise and activation-related percentage signal intensity change. BOLD MR imaging can also be performed with a spin-echo technique, which is less susceptible to inflow effects. However, this method also provides a relatively low contrast-to-noise ratio at 1.5 T (22).

The problem of low contrast-to-noise ratios in inflow-suppressed BOLD GRE imaging and spin-echo functional MR imaging can be overcome by performing these studies at higher field strengths. The T2* effect due to diffusion through internal gradients (eg, deoxygenated hemoglobin) increases with field strength (at least sevenfold, from 1.5 to 4 T) (11). Another way to circumvent the problem of a low signal-to-noise ratio is to use the dynamic MR imaging method. Our data show that the dynamic MR imaging technique is a valuable tool that can be performed with widely available 1.5-T imagers. As more experience is gained with the use of exogenous paramagnetic agents, current limitations may be overcome. Our volunteers received a total of 0.4 mmol/kg gadopentetate dimeglumine as a bolus—four times the normal recommended clinical dose. There were no statistically significant changes in any noninvasive physiologic parameters (postural blood pressure, heart rate, or respiratory rate) in these volunteers. Frank et al (4) reported only mild side effects in a study of 51 patients at this dose, and these effects were no more frequent than those seen at the standard dose.

A promising solution to many of the current limitations involves multi-

Table 3
Percentage of Signal Intensity Change in the Frontal Cortex

	Activation	
Subject	Dynamic MR Imaging	Bold Imaging
1	−7.6	−0.1
2	−2.9	−0.2
3	−14.5	−0.3
4	0.3	−0.9
5	4.8	0.6
Mean ± SD	−4.0 ± 7.4	−0.2 ± 0.5

Note.—Data are given as percentages. SD = standard deviation.

section and three-dimensional volume techniques that would exploit the advantages of both methods (ie, the increased susceptibility effect of an exogenous vascular paramagnetic agent such as gadopentetate dimeglumine coupled with the advantage of repeatability). This may be conceivable in the near future by administering steady-state levels of paramagnetic agents via an intravenous drip. Paramagnetic agents with high relaxivity values and long intraluminal vascular half-lives (eg, iron-oxide compounds) may be best suited for this purpose. ■

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